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PRINCIPAL INVESTIGATOR: **Victoria Risbrough, PhD**

CONTRACTING ORGANIZATION: **Veterans Medical Research Foundation**
San Diego, CA 92161-0002

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Victoria Risbrough, PhD

email: vrisbrough@ucsd.edu

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13. SUPPLEMENTARY NOTES

14. ABSTRACT
PTSD is a growing concern for both active duty personnel and Veterans. Fear conditioning is implicated in the development of PTSD, while successful acquisition, consolidation, and recall of extinction memory are implicated in both the natural reduction of initial PTSD symptoms and as the mechanism underlying the most successful treatment for PTSD, Prolonged Exposure. This project is the first to examine the role of sleep and sleep loss in acquisition, consolidation, and generalization of extinction memory in humans. Our main finding is that sleep loss most strongly affects recall of extinction learning, and that the REM sleep stage is associated with ability to recall extinction as well as recall safety signal learning. These findings suggest that sleep plays a critical role in long term retention of fear inhibition processes, and efforts to support sleep and especially adequate REM during exposure therapy may enhance efficacy and reduce remission after treatment.

15. SUBJECT TERMS
PTSD, sleep deprivation, fear conditioning, extinction memory, humans

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Table of Contents

Introduction

PTSD is a growing concern for both active duty personnel and Veterans. Fear conditioning is implicated in the development of PTSD, while successful acquisition, consolidation, and recall of extinction memory are implicated in both the natural reduction of initial PTSD symptoms and as the mechanism underlying the most successful treatment for PTSD, Prolonged Exposure. In animal models, sleep deprivation has been shown to impair extinction memory. Indirect evidence in humans also supports that notion, but it has never been tested directly in humans. Some of the most ubiquitous and distressing symptoms of PTSD are insomnia and nightmares. The resultant sleep deprivation may actually serve to perpetuate the disorder by interfering with treatments designed to promote extinction memories. Before this hypothesis can be tested in clinical populations, however, well-controlled experimental studies need to establish the exact role of sleep deprivation in extinction acquisition, consolidation, and recall in humans. This study will do just that. This is a mixed-effects study designed to examine the impact of 36 hours TSD on fear conditioning and consolidation (Aim 1), as well as extinction memory acquisition, recall, and generalization (Aim 2). A total of 60 subjects will participate across 3 years. Following recruitment and screening, subjects will spend 4 nights and days in the laboratory: a) adaptation to the lab (Night/Day0); b) normal sleep followed by fear memory acquisition (Night/Day1); c) sleep or TSD followed by fear recall and extinction memory acquisition (Night/Day2); and d) sleep or TSD followed by a test of extinction recall and generalization (Night/Day3). Group1 will receive sleep prior to each testing day, Group2 will be sleep deprived prior to Day2, and Group3 will be sleep deprived prior to Day3.

Body

This report covers the second No Cost Extension year of the project. This year focused on data processing and analysis, as well as dissemination and publication of our findings. Specific activities include:

a. Data Processing. As describe in a series of quarterly reports, we were finally able to continue spending on the project once the PI change was accepted, and hired data cleaners and a statistician to finalize all data cleaning and analysis (EMG and sleep variables).

b. Data Analysis. We have completed our data analysis for our 3rd manuscript, which will be submitted in November to Proceedings of the National Academy of Sciences.

c. Dissemination. Ms. Straus has made national presentations of our study findings.

Straus, L.D., Acheson, D., Risbrough, V.B., & Drummond, S.P.A. (2015 June). The Effect of 36 hours of Total Sleep Deprivation on Extinction Learning and Recall. Oral presentation at the 28th Annual Meeting of the Associated Professional Sleep Societies. Seattle, Washington (see attached slides)

d. Manuscripts. We have published two manuscripts, thus far from this study (reported last year), and will submit a third in November.

e. In addition to the submission of the 3rd paper, we are also currently working on a fourth paper to identify physiological sleep variables that impinge on extinction and safety recall (i.e. sympathetic responding via measures of heart rate variability during sleep).

Key Research Accomplishments

Data collection and analysis of all primary aims completed. Our study findings were presented at sleep conferences (see above). We published two manuscripts and the 3rd manuscript is being submitted in November.

Reportable Outcomes

We are finalizing our 3rd manuscript which we think will provide important new insights into how sleep affects fear extinction. In brief, we found that sleep deprivation before extinction training does not alter learning but does significantly reduce recall of extinction 24 hrs later. We did not find effects of sleep deprivation after extinction learning (before recall), suggesting that sleep before extinction training is the critical component to supporting long term fear inhibition (Figure 1). We also found that the amount of fear inhibition on day 3 (recall testing) was significantly associated with amount of REM consolidation, suggesting that REM sleep in particular may play an important role in retaining fear extinction memory (Figure 2).

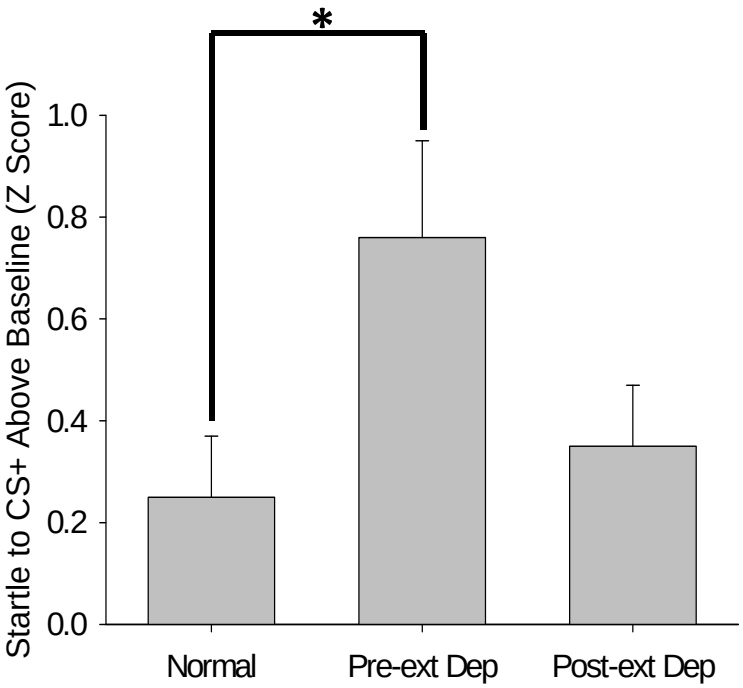

Figure 1: Pre-extinction training sleep deprivation reduces extinction recall. Standardized potentiated startle magnitudes by sleep group across the final recall session (day 3 of testing). *=p<.05 for a priori comparison with the normal sleep group. Normal = normal sleep group; Pre-ext Dep = pre-extinction sleep deprivation group, and Post-ext Dep = post-extinction sleep deprivation group. Note groups did not differ on level of fear conditioning, cued fear recall or extinction training sessions.

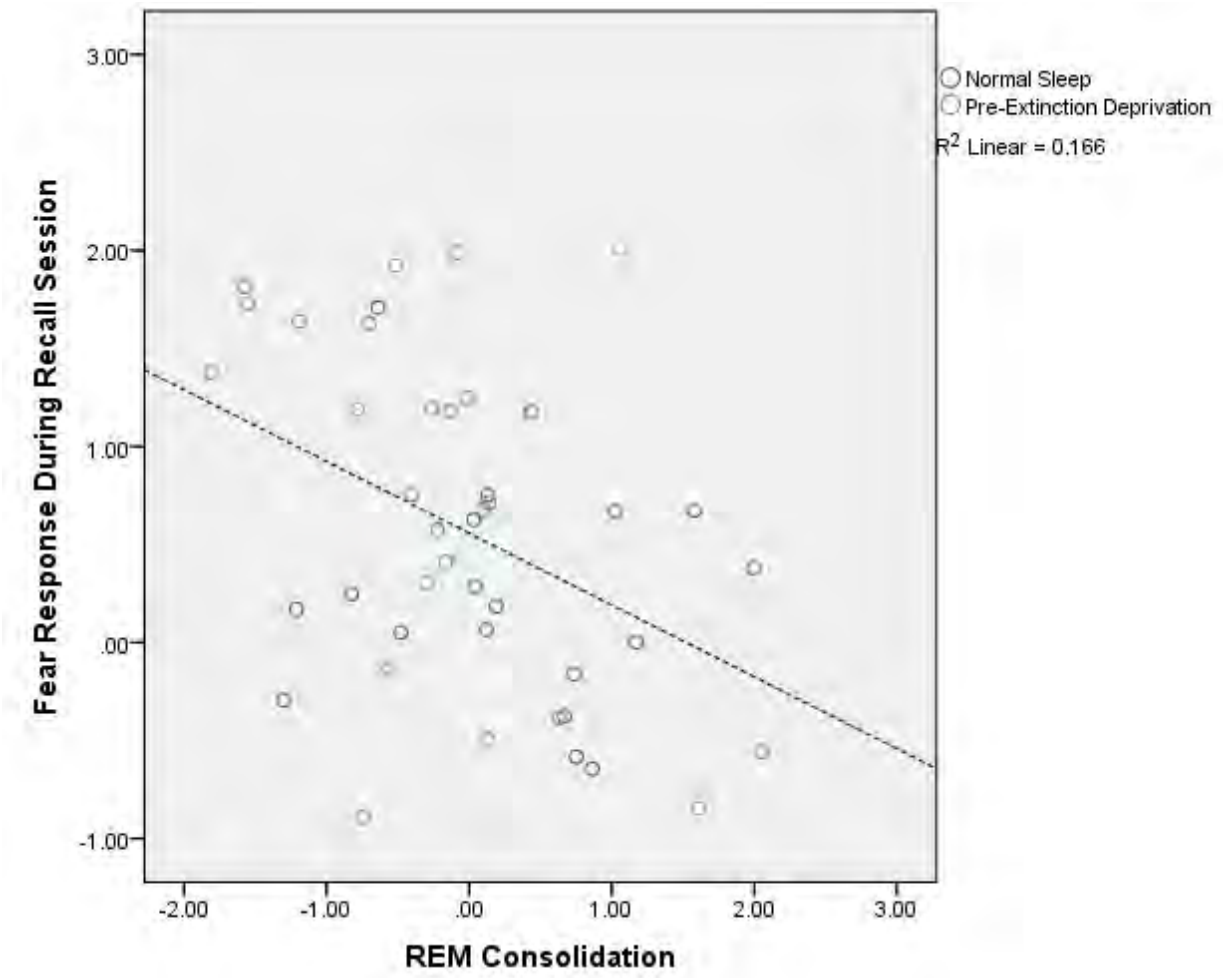

Figure 2: Relationship between REM sleep consolidation on Night 2 and extinction recall on Day 3, by group. Higher scores on REM consolidation on Night 2 corresponded to reduced fear responsiveness to the CS+ on Day 3, indicating enhanced extinction recall.

Conclusion

This past year, we were able to finalize data analysis for two more manuscripts, have reached completion of one manuscript for submission and are actively writing a fourth..

There are two major implications of our findings. First, our finding that sleep deprivation before extinction learning suggests that adequate sleep is critical for retention of extinction recall. This finding has direct implications for exposure-based treatments for PTSD as well as preventing PTSD. In the treatment scenario, poor sleep, especially before exposure therapy sessions, may significant impair the treatment efficacy of exposure therapy by inhibiting retention of an extinction acquired during the session. Second, it implies that poor sleep after trauma exposure may interfere with naturalist extinction learning, which could increase risk for development of PTSD. These data would suggest that prevention of PTSD may lie in part in supporting adequate sleep (and REM consolidation) after trauma exposure. Our data that REM consolidation may play a role in retention of extinction learning also supports the idea that sleep disturbances (e.g. circadian phase shifts) or drug treatments that suppress REM should be avoided after trauma exposure and certainly in subjects undergoing exposure therapy for PTSD.

References

See above

Appendices

Slides of presentations reported in section c.

Supporting Data

N/A

The Effect of 36 hours of Total Sleep Deprivation on Extinction Learning and Recall

Laura D. Straus, MS
Dean Acheson, PhD
Victoria Risbrough, PhD
Sean P.A. Drummond, PhD

Veterans Affairs San Diego Healthcare System
University of California, San Diego

Conflict of Interest Disclosures for Speakers

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Grant/Research Support	
Consultant	
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Sleep and Extinction Learning

- Animal models show fear conditioning:
  - Disrupts sleep
- Disrupted sleep, in turn
  - Impairs extinction (unlearning of fear)
  - Impairs ability to retain extinction learning
- In humans, PTSD involves:
  - Sleep disruption
  - Impaired fear and extinction processes
- Few human studies examining the effect of sleep disruption on extinction processes

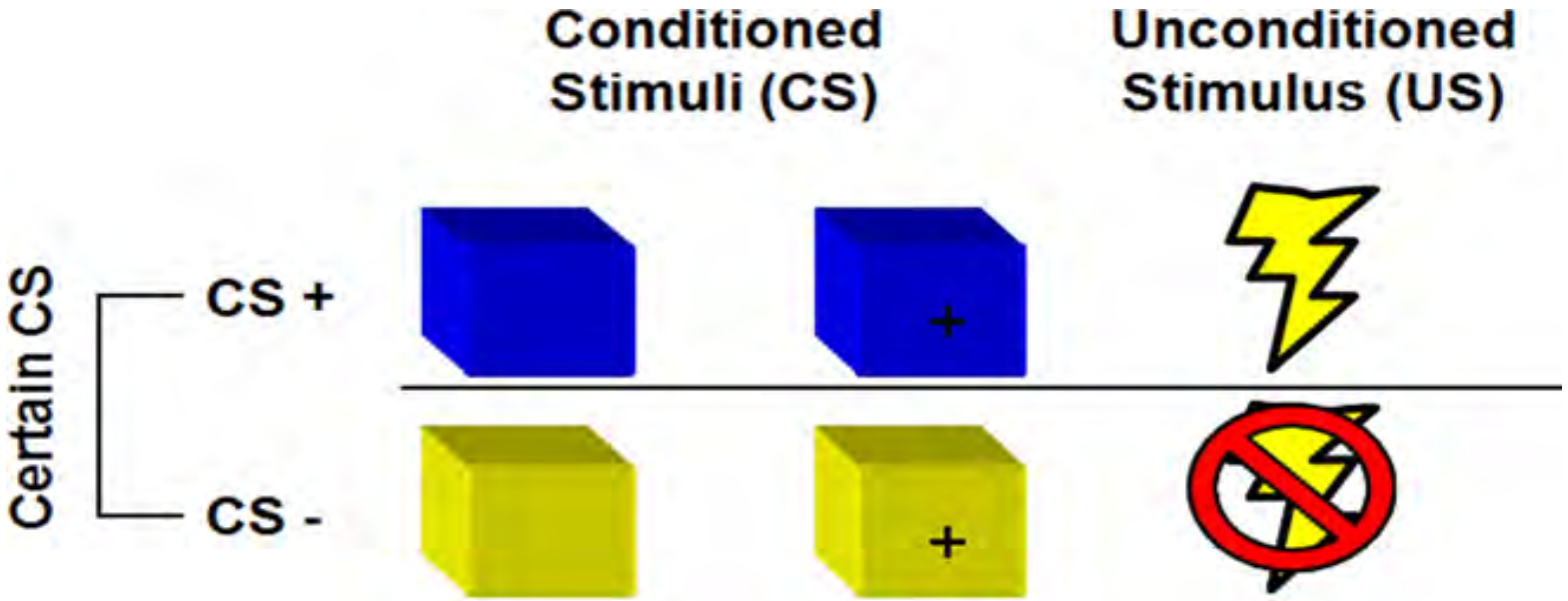
Aims and Hypotheses

- Aim
  - Translational study examining impact of total sleep deprivation (TSD) on extinction learning and recall

- Hypotheses
  - TSD may impair extinction learning
  - TSD will impair extinction recall

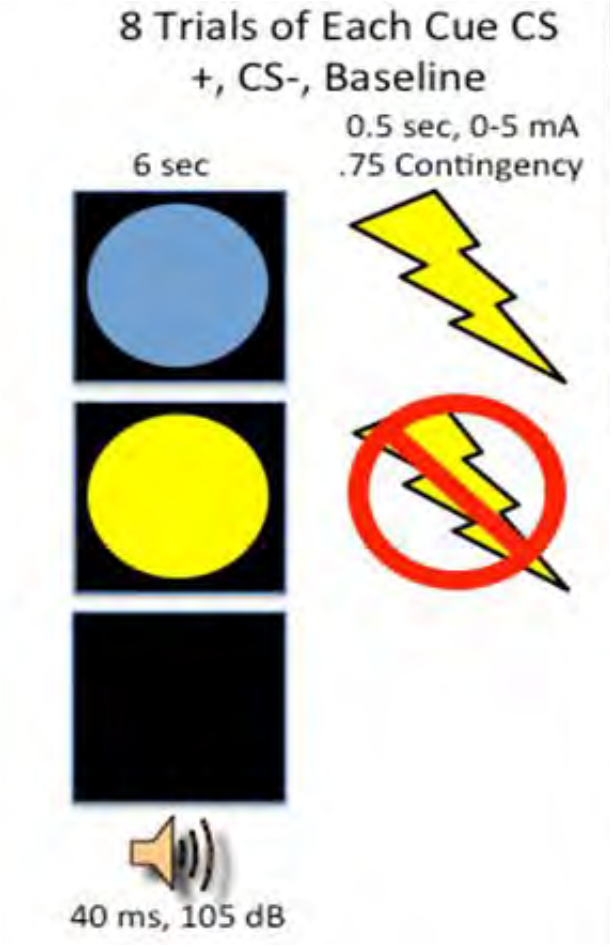
What is Fear Learning?

- Pair neutral stimulus (blue square) with aversive stimulus (shock) → threat signal
- Do not pair stimulus (yellow square) with shock → safety signal

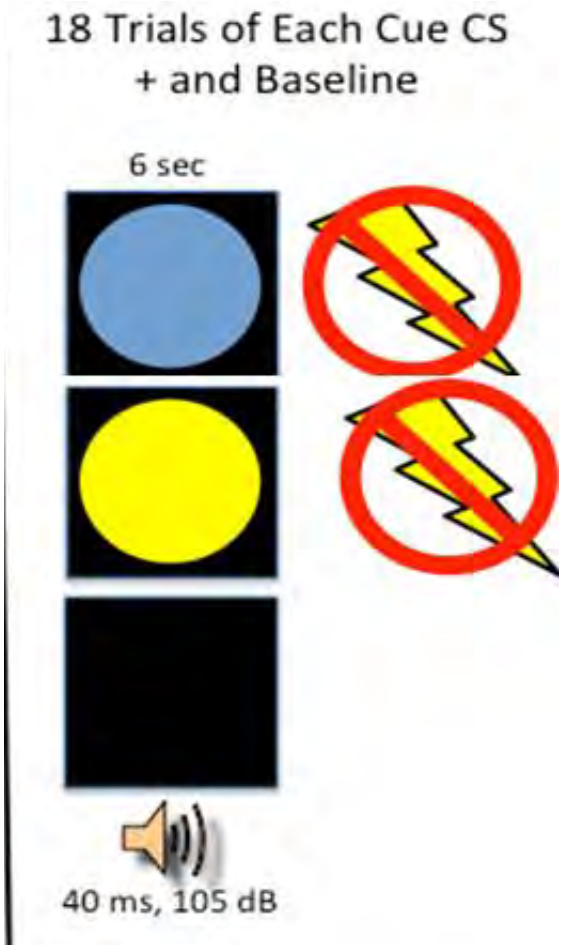


+Startle Task Paradigm

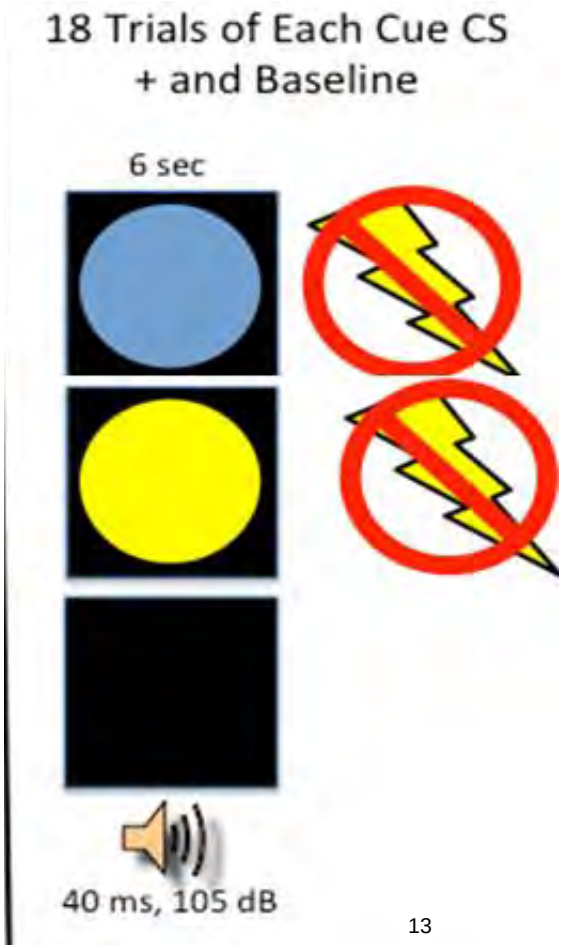
Fear Conditioning Phase (Day 1)



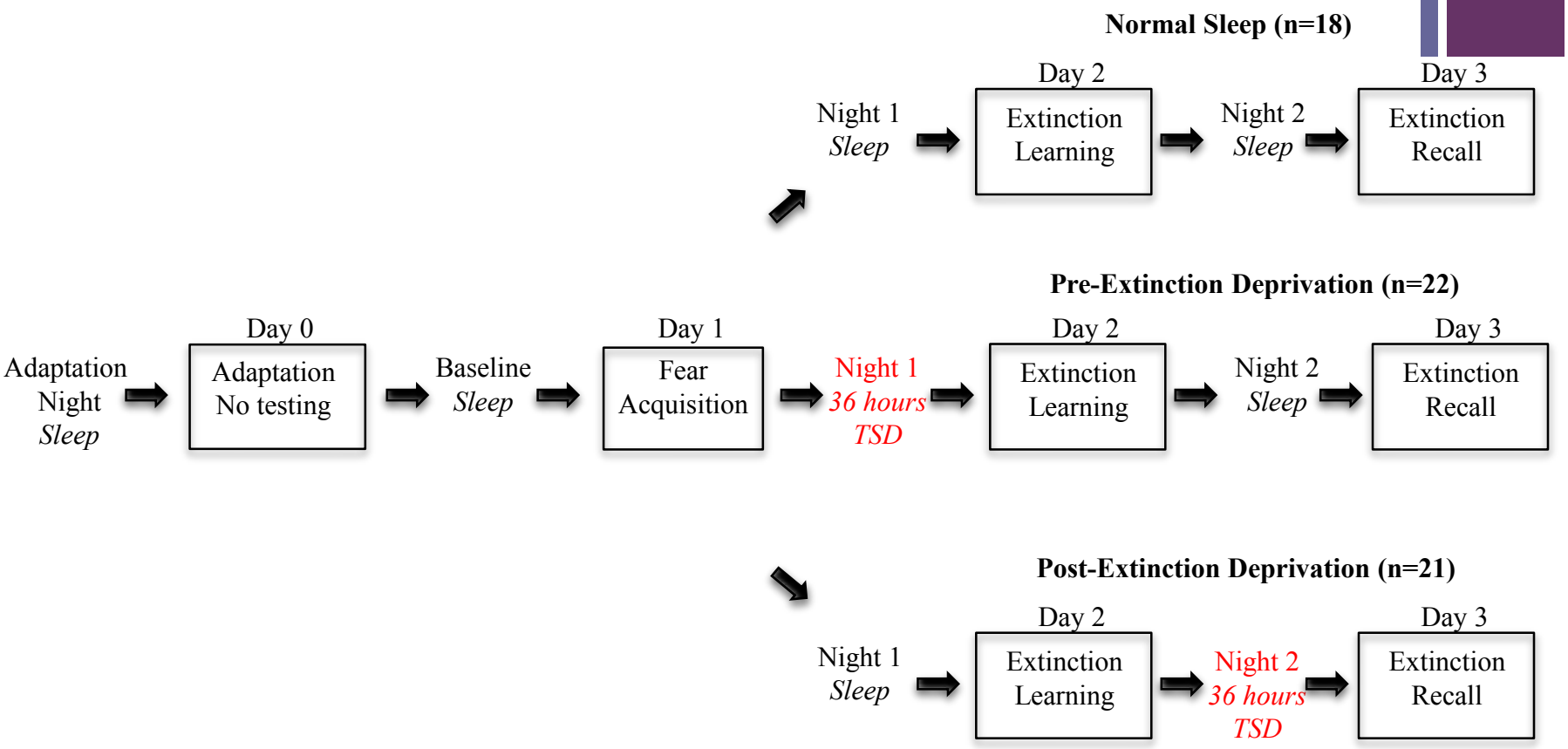
Extinction Learning (Day 2)



Extinction Recall (Day 3)



+Methods



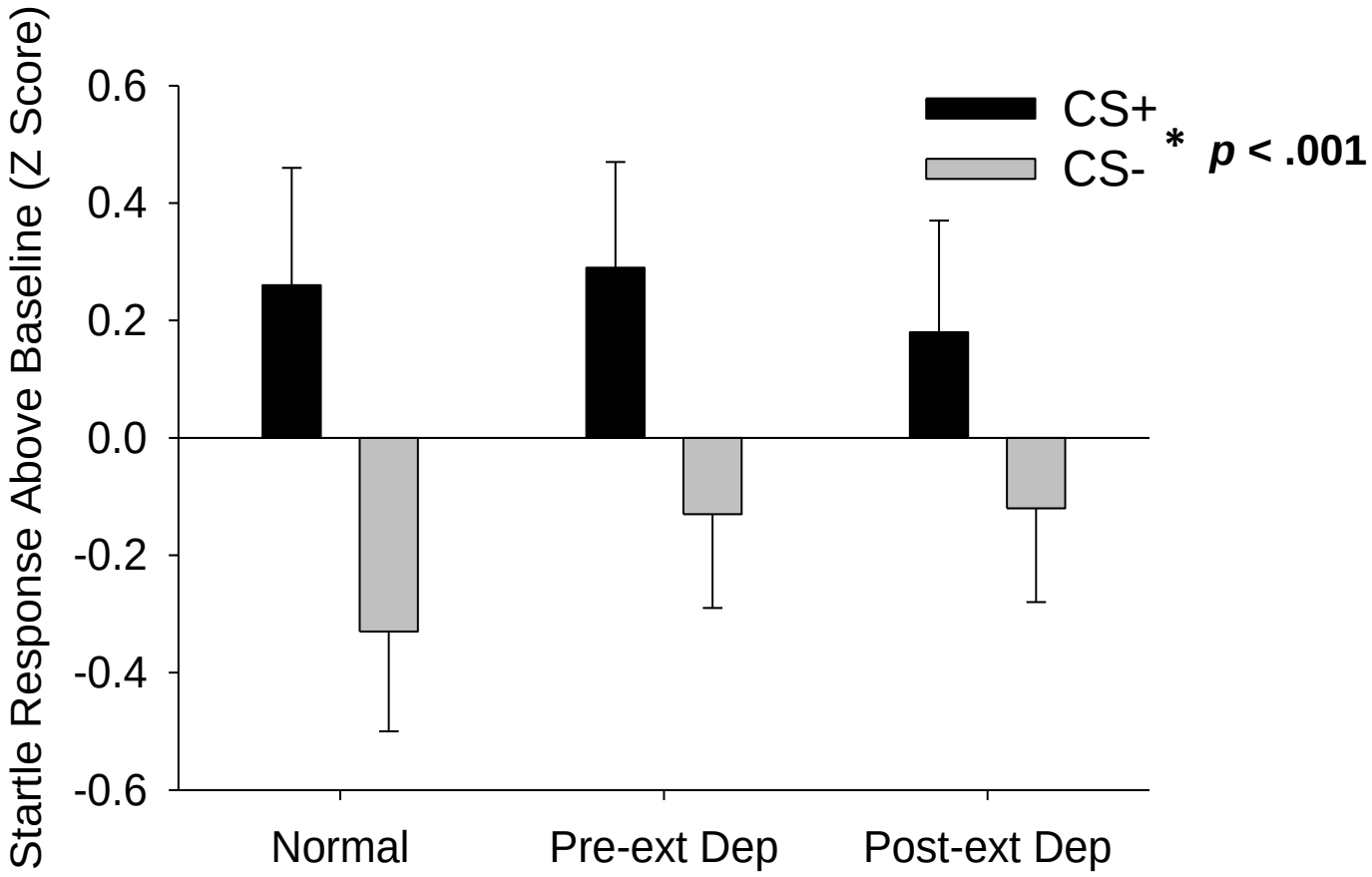
Testing was scheduled in the evening each day, 10-12 hours after participants' habitual wake time

Subjects & Analyses

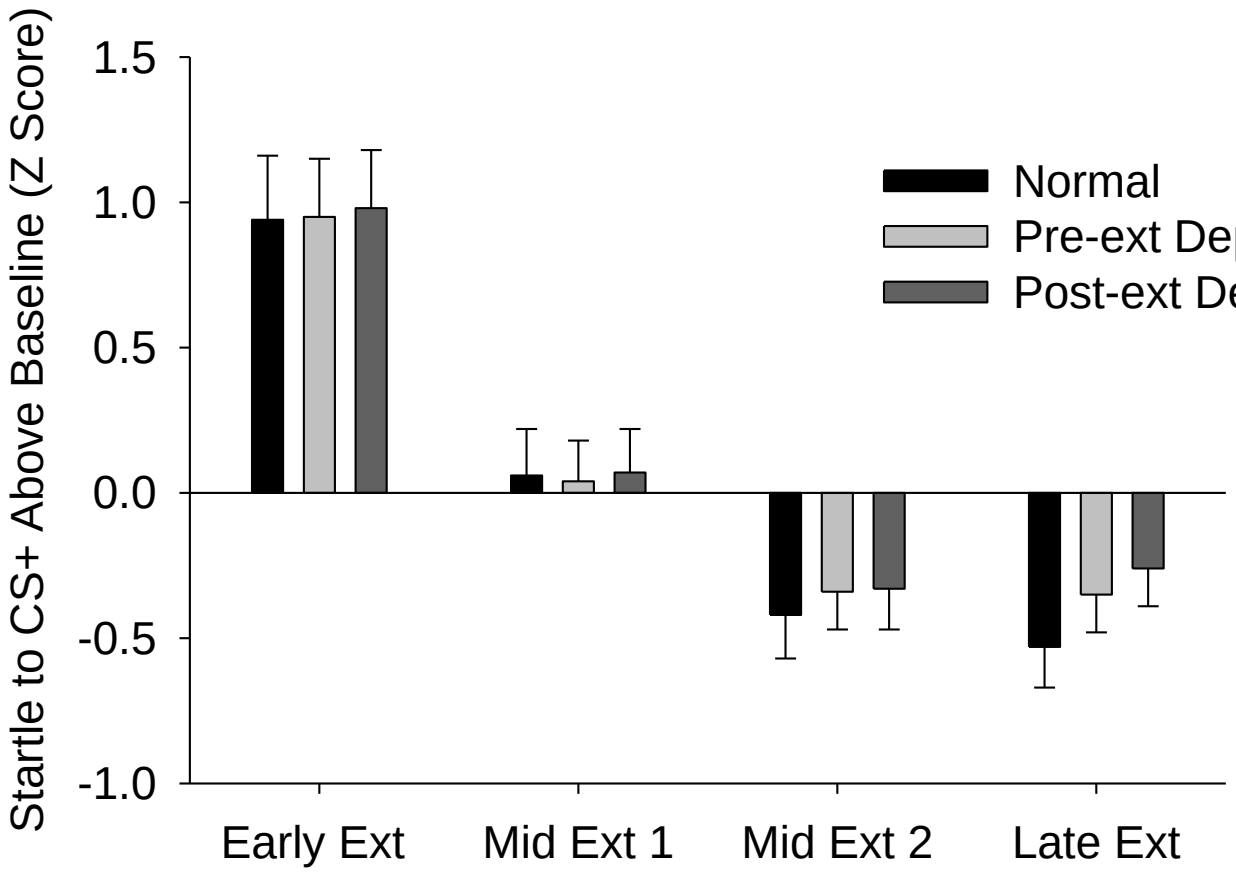
- Subjects (n=61)
  - Age: 23.9 ± 4.6 (range 18-38 y.o.)
  - 39% female
  - Recruited through Internet advertisements, flyers on campus, and word of mouth
  - Screened to be physically healthy and without mental health conditions
  - Sleep regulated 1 week prior to entering lab
  - Restricted from caffeine/alcohol 48 hours prior to lab

- Analyses
  - Independent samples t-tests to compare
    - Control versus TSD during extinction learning
    - Control versus TSD during extinction recall

Results—Fear Conditioning

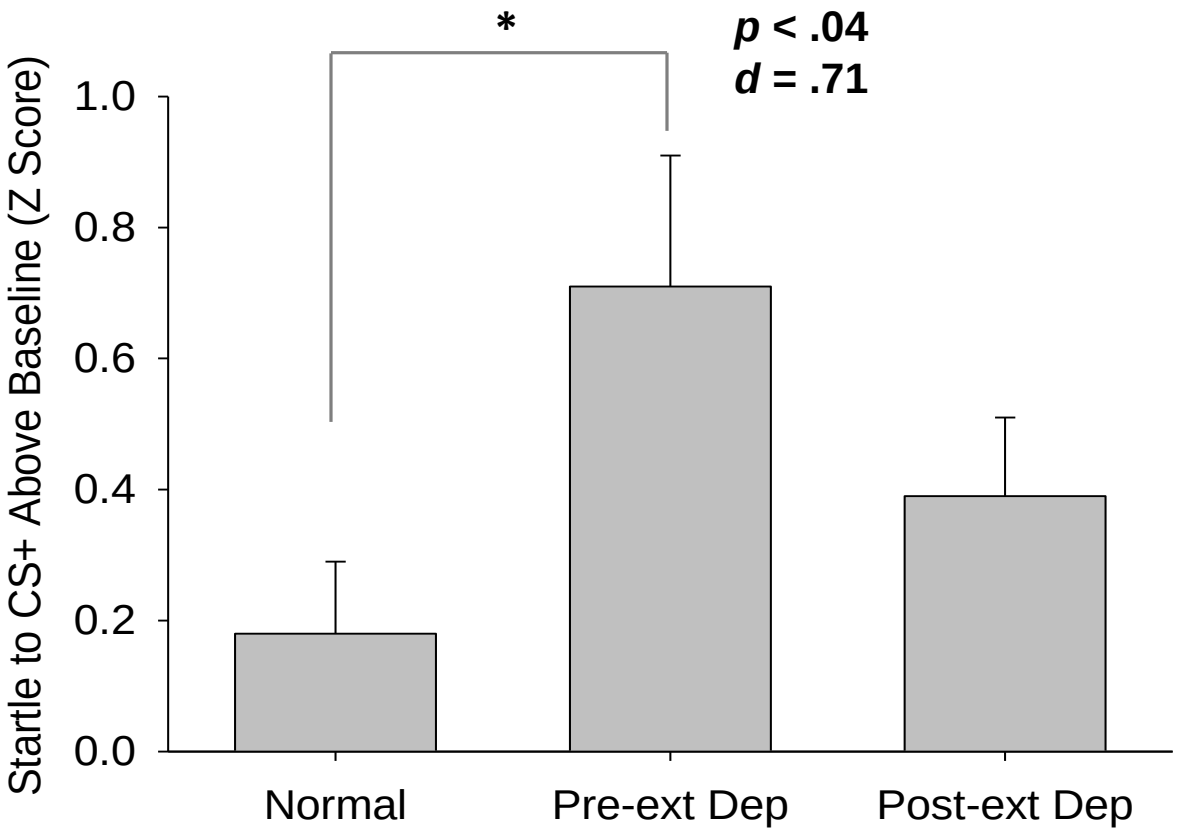


Results—Extinction Learning



***F*s < 1, ns**

Results—Extinction Recall



+Conclusions

- Sleep Disruption and Extinction Processes
  - TSD prior to extinction did not affect extinction learning
  - TSD prior to extinction affected recall of extinction
- PTSD
  - Disrupted sleep & nightmares
  - Re-experiencing symptoms in response to trauma-related cues
  - Disrupted sleep may perpetuate the disorder and/or interfere with treatment response
  - Treating sleep = ↑ response to PTSD treatment

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